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RESEARCH

Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study

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Abstract

Objective To determine the independent associations of antihypertensive drugs with the risk of incident gout among people with hypertension.

Design Nested case-control study.

Setting UK general practice database, 2000-7.

Participants All incident cases of gout (n=24 768) among adults aged 20-79 and a random sample of 50 000 matched controls.

Main outcome measure Relative risk of incident gout associated with use of antihypertensive drugs.

Results After adjusting for age, sex, body mass index, visits to the general practitioner, alcohol intake, and pertinent drugs and comorbidities, the multivariate relative risks of incident gout associated with current use of antihypertensive drugs among those with hypertension (n=29 138) were 0.87 (95% confidence interval 0.82 to 0.93) for calcium channel blockers, 0.81 (0.70 to 0.94) for losartan, 2.36 (2.21 to 2.52) for diuretics, 1.48 (1.40 to 1.57) for β blockers, 1.24 (1.17 to 1.32) for angiotensin converting enzyme inhibitors, and 1.29 (1.16 to 1.43) for non-losartan angiotensin II receptor blockers. Similar results were obtained among those without hypertension. The multivariate relative risks for the duration of use of calcium channel blockers among those with hypertension were 1.02 for less than one year, 0.88 for 1-1.9 years, and 0.75 for two or more years and for use of losartan they were 0.98, 0.87, and 0.71, respectively (both P<0.05 for trend).

Conclusions Compatible with their urate lowering properties, calcium channel blockers and losartan are associated with a lower risk of incident gout among people with hypertension. By contrast, diuretics, β blockers, angiotensin converting enzyme inhibitors, and non-losartan angiotensin II receptor blockers are associated with an increased risk of gout.

Introduction

Hypertension is one of the most common comorbidities of gout. According to the latest estimates from the US National Health and Nutrition Examination Survey (2007-8), 74% of patients with gout have hypertension,[1] which corresponds to 6.1 million adults in the United States alone. This substantial burden of comorbidity possibly stems from copathogenesis of the two conditions or renal changes in hypertension leading to decreased urate excretion. Studies have shown that the presence of hypertension is independently associated with the risk of incident gout[2] through reduced renal blood flow with increased renal and systemic vascular resistance and decreased renal excretion of urate.[3-6]

Certain antihypertensive drugs also increase the levels of serum uric acid and thus may contribute to the risk of gout. For example, in addition to the well known entities of diuretic induced hyperuricaemia and gout,[3 7 8] the use of β blockers has been shown to increase levels of serum uric acid in short-term trials.[8 9] However, calcium channel blockers and losartan have been found to lower serum uric acid levels,[10-16] carrying the potential to lower the risk of gout. To date, however, no study has investigated the relation between various antihypertensive agents and the risk of gout. To address these issues, we analysed a cohort of 24 768 people with newly diagnosed gout and 50 000 matched controls from the health improvement network database.

Methods

Study population

The health improvement network database contains computerised medical records entered by general practitioners in the United Kingdom.[17] Data on about four million patients are systematically recorded and sent anonymously to the database. Patients included in the database are representative of the UK population for age, sex, and geographical region.[17] The health improvement network collects and organises this information for the purpose of research projects. The

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computerised information includes personal characteristics of the patients, details of visits to general practitioners, diagnoses from referrals to specialists and hospital admissions, results of laboratory tests, and a free text section (information available on request). Diagnoses are recorded using READ codes.[18 19] Prescriptions issued by primary care providers are recorded automatically in the database; drugs are coded using the Multilex classification (www.firstdatabank.co.uk/8/multilex-drug-data-file). An additional requirement for participating practices is to record the indication for new courses of treatment. The validity of the database for pharmacoepidemiological research has been shown.[20]

We carried out a nested case-control study using data from the health improvement network database between January 2000 and December 2007. The source population included all adults aged 20-89 with permanent registration status or who had died in the last update of the database. Study cohort members were required to have been enrolled with their general practitioner for two or more years, had at least one visit to their general practitioner, and had at least one prescription in the two years before entering the study. The start date corresponded to the date when all of these eligibility criteria had been met. People had to be free of gout and cancer before entering the study. All participants in the study cohort were followed up and contributed person time from their respective start date until the earliest of one of the following end points: detection of gout, 90th birthday, death, or end of study period, whichever came first. The final cohort encompassed 1 775 505 people followed for an average of 5.2 years.

Ascertainment of gout

From an automatic search using READ codes we identified all people with a first ever diagnosis of gout recorded by a general practitioner. The date of gout onset (index date) was defined as the date of either the first diagnosis of gout or the first anti-gout treatment (allopurinol, colchicine, or uricosuric drugs), whichever came first, among those with a diagnosis of gout. We considered incident cases as those who had an index date (gout onset) occurring after the date of entry to the study cohort (n=24 768).

To evaluate the robustness of gout ascertainment, we carried out a sensitivity analysis restricting people with gout to those receiving anti-gout treatment. To this end we used the following operational definition: identified within 90 days of a first ever diagnosis of gout (index date), any anti-gout treatment (colchicine, probenecid, or uricosuric drugs), or a prescription of a non-steroidal anti-inflammatory drug on the same index date. A similar case definition of gout has been shown to have a validity of 90% in the general practice research database.[21 22]

Control sampling

From the same study cohort where we ascertained gout cases we sampled 50 000 controls that were frequency matched on age, sex, and calendar year. We applied the same exclusion criteria to controls as to cases. This was done by generating at random a date encompassed within the study period for each member of the study population. If the random date for a study member was included in his or her eligible person time (follow-up period), we chose that person as an eligible control and we used the random date as their index date.

Use of antihypertensive drugs

We evaluated the potential impact of antihypertensive drugs by class: diuretics, β blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, losartan, and non-losartan angiotensin II receptor blockers. Since previous literature has suggested that, unlike other angiotensin II receptor blockers, losartan shows urate lowering properties,[12 13] we evaluated its individual effect separately from other angiotensin II receptor blockers. We classified use of antihypertensive drugs into four mutually exclusive usage groups: current use (the supply of the most recent prescription lasted until the index date or ended in the 30 days before that date), recent use (the supply of the most recent prescription ended between 31 and 365 days before the index date), past use (the supply of the most recent prescription ended more than 365 days before the index date), and never use (no recorded use at any time before the index date). Duration of treatment was calculated among current users of drugs, which we computed by summing the time of consecutive prescriptions (allowing for an maximum interval of 60 days between the end of one prescription and the start of another). To analyse potential dose effects we used information on dose from the *British National Formulary* (http://bnf.org/bnf/index.htm) and classified dose of antihypertensive drug into three groups: medium or low (recommended starting doses or lower), high (higher than recommended starting doses), and unknown.

Covariate assessment

From the database we collected data on personal characteristics and lifestyle factors such as alcohol use, smoking, and body mass index, as well as comorbidities such as ischaemic heart disease, hypertension, hyperlipidaemia, renal failure, and heart failure before the index date. The presence of these comorbidities was defined using READ codes for diagnosis as recorded by the general practitioners. We also ascertained the numbers of visits to a general practitioner, referrals, and admission to hospital in the year before the index date.

Statistical analysis

Using unconditional logistic regression we estimated the odds ratios and 95% confidence intervals for gout associated with use of calcium channel blockers, losartan, and other antihypertensive drug classes. Our multivariate analyses were adjusted for the frequency matched variables, visits to a general practitioner, and the covariates of body mass index (five categories), alcohol use (six categories), smoking (four categories), ischaemic heart disease, hypertension, hyperlipidaemia, and renal failure. To estimate the independent impact of each drug class, even among those who used a combination of antihypertensive drug classes, we simultaneously adjusted these regression models for each antihypertensive drug class. In addition we examined associations with relatively common combinations of antihypertensive treatment in our study population (>3% prevalence of use among users of antihypertensives) compared with no antihypertensive use while adjusting for other combinations and the same set of covariates. Under our study design the odds ratio is an unbiased estimator of the incidence rate ratio and we have reported odds ratio estimates as relative risks throughout this paper. We calculated absolute risk differences by applying these relative risks to the incidence rates of gout derived from our underlying cohort. We carried out stratified analyses by presence of hypertension to explore potential differences in the impact of antihypertensive drugs depending on the presence of hypertension and to help isolate the impact of particular antihypertensives. We tested the significance of the interaction with a likelihood ratio test by introducing the interaction term to our final model with the main terms.

Results

The study included 24 768 patients with newly diagnosed gout and 50 000 controls; table 1⇓ shows their characteristics, stratified by the presence of hypertension. In both groups gout was associated with an increased number of visits to a general practitioner, alcohol use, adiposity, ischaemic heart disease, hyperlipidaemia, and renal failure. In total, 12 858 (51.9%) patients with gout had a recorded diagnosis of hypertension before the diagnosis of gout. After adjusting for age, sex, calendar year, and visits to a general practitioner, the relative risk for incident gout among those with hypertension was 1.99 (95% confidence interval 1.92 to 2.06) compared with those without hypertension. After further adjustment for other covariates, this relative risk was attenuated but remained significant (1.75, 1.69 to 1.82).

Compared with no use of calcium channel blockers, current use among people with hypertension was associated with a lower risk of developing gout (table 2⇓). After adjusting for age, sex, calendar year, and visits to a general practitioner, the relative risk for gout among those currently using calcium channel blockers was 0.95 (0.90 to 1.00). After adjusting for other covariates and other antihypertensive drugs, the multivariate relative risk was 0.87 (0.82 to 0.93). (The corresponding absolute risk difference was 60 cases per 100 000 person years.) The multivariate relative risks for individual calcium channel blockers were 0.79 (0.73 to 0.86) for amlodipine, 0.87 (0.78 to 0.97) for nifedipine, and 0.86 (0.75 to 0.99) for diltiazem. The associations were similar among people without hypertension (P=0.17 for interaction, table 2). The multivariate relative risks for calcium channel blockers according to duration of use among those with hypertension were 1.04 for less than one year, 0.89 for 1-1.9 years, and 0.77 for two or more years (95% confidence interval 0.71 to 0.83, P<0.001 for trend, table 3⇓). The inverse association was stronger with high dose use of calcium channel blockers than with medium or low dose use (multivariate relative risk 0.80 *v* 0.90; P=0.02, table 4⇓).

Similarly, current use of losartan among those with hypertension was associated with a lower risk of developing gout (multivariate relative risk compared with no use of losartan was 0.81, 0.70 to 0.94, table 2). (The corresponding absolute risk difference was 86 cases per 100 000 person years.) The association was not significantly different among those without hypertension (P=0.20 for interaction), but the frequency of losartan use in the group without hypertension was low (table 2). The multivariate relative risks according to duration of use among those with hypertension were 0.97 for less than one year, 0.86 for 1-1.9 years, and 0.70 for two or more years (0.57 to 0.86, P=0.02 for trend, table 3). The inverse association tended to be stronger with high dose use of losartan than with medium or low dose use (multivariate relative risk 0.66 *v* 0.88; P=0.06, table 4).

In contrast, current use of diuretics, β blockers, angiotensin converting enzyme inhibitors, and non-losartan angiotensin II receptor blockers among those with hypertension were all associated with an increased risk of developing gout. Compared with no use of diuretics, current use was associated with the greatest multivariate relative risk (2.36, 2.21 to 2.52). The corresponding multivariate relative risks of incident gout were 1.48 (1.40 to 1.57) for β blockers, 1.24 (1.17 to 1.32) for angiotensin converting enzyme inhibitors, and 1.29 (1.16 to 1.43) for non-losartan angiotensin II receptor blockers (table 2). (The respective absolute risk differences were 572, 218, 109, and 132 cases per 100 000 person years.) These multivariate relative risks tended to increase with increasing duration of use among those with hypertension (P<0.05 for trend) except for β blockers and non-losartan angiotensin II receptor blockers (table 3). These associations tended to be stronger with higher doses than with medium or low doses, except for angiotensin converting enzyme inhibitors (table 4). Overall, these relative risks tended to be similar among those without hypertension except for the relation between duration of use and non-losartan angiotensin II receptor blockers. Notably, the frequency of such use in this group was low.

In our sensitivity analysis, restricting gout cases to those receiving anti-gout treatment (n=19 749), the multivariate relative risks of incident gout associated with current use of antihypertensive drugs among those with hypertension (n=10 195) were 0.87 (0.82 to 0.93) for calcium channel blockers, 0.78 (0.67 to 0.92) for losartan, 2.35 (2.19 to 2.53) for diuretics, 1.49 (1.40 to 1.59) for β blockers, 1.25 (1.17 to 1.33) for angiotensin converting enzyme inhibitors, and 1.31 (1.17 to 1.47) for non-losartan angiotensin II receptor blockers.

The direction and magnitude of associations with common combination therapy were consistent with those from options for monotherapy. In commonly used dual therapy options that included diuretics, the multivariate relative risks for incident gout compared with no use of antihypertensives were larger with angiotensin converting enzyme inhibitors (3.17, 2.90 to 3.47) and with β blockers (3.33, 3.03 to 3.66) than with calcium channel blockers (2.11, 1.87 to 2.38). Similarly, in combined use of β blockers, the corresponding relative risk with angiotensin converting enzyme inhibitors (1.70, 1.48 to 1.96) tended to be larger than that with calcium channel blockers (1.24, 1.07 to 1.96), whereas the relative risk for the combination of angiotensin converting enzyme inhibitors and calcium channel blockers was not significant (1.13, 0.96 to 1.32). Similarly, in triple combination therapy options that included both diuretics and angiotensin converting enzyme inhibitors, the multivariate relative risks for incident gout were larger with β blockers (3.88, 3.43 to 4.38) than with calcium channel blockers (2.30, 2.01 to 2.63). Notably, the multivariate relative risk for the combined use of calcium channel blockers and losartan was 0.66 (0.39 to 1.13), but the frequency of combined use was low (<1%).

Discussion

In this large general practice cohort representative of the UK population, we found that use of calcium channel blockers and losartan was associated with a moderately lower risk of incident gout among patients with hypertension. These associations were independent of use of other evaluated antihypertensive drugs and other risk factors for gout such as age, body mass index, smoking, alcohol use, and presence of ischaemic heart disease, hyperlipidaemia, hypertension, and renal failure. These inverse associations were stronger with both a longer duration and a higher dose of use. In contrast, we found that use of diuretics, β blockers, angiotensin converting enzyme inhibitors, and non-losartan angiotensin II receptor blockers was associated with an increased risk of incident gout among patients with hypertension. The magnitude of relative risk was strong with diuretic use and more moderate with the other antihypertensive drugs. These associations were also independent of use of other antihypertensives and other risk factors for gout and tended to become stronger with a longer duration of use and a higher dose. The absolute risk difference was the largest with diuretic use (about six cases per 1000 person years) and more moderate with the other agents (one or two cases per 1000 person years). The current study provides the first large scale evidence for the

independent differential effect of antihypertensive drugs for and against the risk for gout.

The inverse association between use of calcium channel blockers and risk of incident gout possibly stems from its action on renal function. An increase in uric acid excretion has been observed with calcium channel blockers.[11-13] Calcium channel blockers could increase the glomerular filtration rate and consequently the clearance rates of uric acid and creatinine. For example, amlodipine has been found to increase the output of fluid from the proximal tubules, as shown by the significant decrease observed in the fractional proximal reabsorption of sodium and the corresponding increase in the reabsorption of sodium in the distal tubule[11] Furthermore, nifedipine, which possesses renal vasodilatory effects,[23] has been found to reduce serum uric acid levels compared with a placebo in the A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) trial (n=7665).[10] Our data indicate that these amlodipine and nifedipine effects on serum uric acid levels can be translated into 21% and 13% decreased risks of gout, respectively, and a similar protective association can be expected from diltiazem as well.

Losartan reduces serum uric acid levels by 20-25% by producing a uricosuric effect in healthy volunteers, patients with hypertension, and transplant recipients.[12 13 15 16 24-26] The uricosuric effect of losartan has been described to be similar to that observed with classic uricosuric agents such as probenecid.[12 13] However, this uricosuric mechanism does not seem to be related to angiotensin II antagonism, as other angiotensin II antagonists do not share the property. For example, other angiotensin II antagonists, including valsartan 80 mg once daily,[27-30] candesartan 8-16 mg daily,[31] telmisartan[32] irbesartan,[24 33] and eprosartan 600 mg[34-36] do not increase uricosuria and thus do not decrease serum uric acid levels.[8] Similarly, angiotensin converting enzyme inhibitors have not been associated with lower serum uric levels.[16] Several experiments, including a Xenopus oocyte model of urate transport injected with URAT1-encoding RNA,[37] have indicated that losartan can directly inhibit URAT1 from the apical side of tubular cells through cis-inhibition as with other uricosuric compounds such as probenecid and benzbromarone.[3 37 38] These data suggest that URAT1 could be the key action site of losartan, as with other uricosuric agents.

We found that other antihypertensive drugs were associated with an increased risk of incident gout. Diuretics increase the net reabsorption of uric acid in the proximal tubule of the nephron and thereby reduce urinary excretion and increase the risk of hyperuricaemia[7 8] and gout.[2] The increase in serum uric acid concentration and the risk of gout caused by diuretics may be noted within a few days of the start of treatment.[39 40] Although not as impressive as the hyperuricaemic property of diuretics, β blockers, including propranolol, atenolol, metoprolol, timolol, and alprenolol, also have been shown to increase serum uric acid levels.[8 9] For example, atenolol 50-100 mg daily for 12 weeks increased uric acid levels by 0.5 mg/dL[41] and the addition of propranolol was associated with a 0.3 mg/dL increase of serum uric acid levels.[42] The mechanism of these urate raising effects of β blockers remains unknown as the data on the effects of β blockers on renal urate excretion have been unclear. For example, whereas single doses of atenolol, propranolol, and tertatolol did not modify the renal clearance of uric acid or the 24 hour urinary excretion of uric acid in healthy people,[42] propranolol was found to reduce the mean renal clearance of uric acid in patients with hypertension.[43]

Clinical and public health implications

Our findings may have practical implications in the management of hypertension, particularly among those who are at a higher risk of developing gout. Our data suggest that calcium channel blockers or losartan would be preferred to other antihypertensive drugs if prevention of gout is relevant and other determining factors are comparable. Furthermore, from a public health perspective, using these urate lowering antihypertensive drugs could help reduce the high comorbidity burden of gout and hypertension.[1] As our findings are based on the reference point of no use of each corresponding antihypertensive drug, the difference in risk of gout between urate lowering agents (for example, losartan) compared with urate raising agents (for example, thiazide) would be even greater, which could in turn lead to noteworthy differences in risk-benefit ratios, particularly in populations at high risk for gout.

Strengths and limitations of the study

This study was carried out using a large UK general practice population; therefore, findings are likely to be applicable to the general population. As antihypertensive drugs are used for other clinical conditions, the overall consistency of the results stratified by hypertension helped to sort out potential drug effects from those of the underlying conditions. Because the definition of gout was based on doctors' diagnoses, a certain level of misclassification of use is inevitable. A diagnosis of gout could often have been recorded based on the suggestive clinical presentation of gout without documentation of monosodium urate crystals. However, any non-differential misclassification of these diagnoses would have biased the study results toward the null and would not explain the strong associations and dose-response relations observed in this study. Furthermore, when we used doctors' diagnoses of gout combined with anti-gout drug use (which showed a validity of 90%[21 22]) as our case definition, our results remained almost identical. Despite the large size of the study cohort, the number of participants in certain subgroups (for example, use of angiotensin II receptor blockers in the group without hypertension or various combination therapy options) was relatively small, which limited our ability to obtain robust estimates. Replicating these results in the context of a larger prospective cohort would be valuable. Such a larger study context would also be useful for quantifying the effects of switching antihypertensive drugs.

Conclusions

Our findings suggest that calcium channel blockers and losartan may be protective against the risk of gout among people with hypertension. These data are compatible with previous findings that suggested these drugs have urate lowering properties. In contrast, diuretics, β blockers, angiotensin converting enzyme inhibitors, and non-losartan angiotensin II receptor blockers are associated with an increased risk of gout. These data may have practical implications for choosing the appropriate antihypertensive drugs in patients with hypertension, a common comorbidity of gout.

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What is already known on this topic

Hypertension is a common comorbidity of gout, affecting up to 74% of patients with gout

Unlike other antihypertensives, calcium channel blockers and losartan may reduce the risk of gout by lowering urate acid levels

No study has, however, investigated this potential link

What this study adds

Compatible with their urate lowering properties, calcium channel blockers and losartan are associated with a lower risk of incident gout among people with hypertension

By contrast, diuretics, β blockers, angiotensin converting enzyme inhibitors, and non-losartan angiotensin II receptor blockers are associated with an increased risk of gout

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Ethical approval: This study was approved by the National Health Service research ethics committee (09/H0305/75).

Data sharing: No additional data available.

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Tables

Table 1| Characteristics of cases of gout and frequency matched controls stratified by presence of hypertension

	Hypertension			No hypertension		
Variables	No (%) of controls (n=16 280)	No (%) of cases (n=12 858)	Relative risk* (95% CI)	No (%) of controls (n=33 720)	No (%) of cases (n=11 910)	Relative risk* (95% CI)
Men	10 898 (66.94)	8431 (65.57)	—	26 055 (77.27)	9515 (79.89)	—
Women	5382 (33.06)	4427 (34.43)	—	7665 (22.73)	2395 (20.11)	—
Age (years):						
20-49	1012 (6.22)	1160 (9.02)	—	9199 (27.28)	4130 (34.68)	—
50-59	2366 (14.53)	2202 (17.13)	—	7745 (22.97)	2671 (22.43)	—
60-69	4410 (27.09)	3423 (26.62)	—	7520 (22.30)	2330 (19.56)	—
70-79	5628 (34.57)	4064 (31.61)	—	6268 (18.59)	1794 (15.06)	—
80-89	2864 (17.59)	2009 (15.62)	—	2988 (8.86)	985 (8.27)	—
No of visits to general practitioner:						
0-4	3743 (22.99)	1822 (14.17)	1	18 957 (56.22)	4963 (41.67)	1
5-9	4957 (30.45)	3414 (26.55)	1.33 (1.23 to 1.43)	8244 (24.45)	3278 (27.52)	1.59 (1.51 to 1.68)
10-19	5425 (33.32)	4911 (38.19)	1.70 (1.58 to 1.82)	4997 (14.82)	2489 (20.90)	2.08 (1.95 to 2.21)
≥20	2155 (13.24)	2711 (21.08)	2.31 (2.12 to 2.51)	1522 (4.51)	1180 (9.91)	3.26 (2.99 to 3.56)
Smoking:						
Non-smoker	8239 (50.61)	6074 (47.24)	1	15 793 (46.84)	5484 (46.05)	1
Current smoker	2500 (15.36)	1516 (11.79)	0.78 (0.73 to 0.84)	7431 (22.04)	2266 (19.03)	0.82 (0.77 to 0.87)
Former smoker	4879 (29.97)	4901 (38.12)	1.16 (1.10 to 1.22)	6000 (17.79)	3050 (25.61)	1.24 (1.17 to 1.31)
Unknown	662 (4.07)	367 (2.85)	1.06 (0.92 to 1.22)	4496 (13.33)	1110 (9.32)	0.90 (0.83 to 0.97)
Alcohol intake (units/wk)†:						
Non-use	6457 (39.66)	4593 (35.72)	1	9939 (29.48)	3035 (25.48)	1
1-9	4612 (28.33)	3371 (26.22)	1.09 (1.02 to 1.15)	8750 (25.95)	2589 (21.74)	0.99 (0.94 to 1.06)
10-24	2593 (15.93)	2544 (19.79)	1.49 (1.39 to 1.60)	5557 (16.48)	2530 (21.24)	1.54 (1.44 to 1.65)
25-42	751 (4.61)	963 (7.49)	1.91 (1.72 to 2.14)	1401 (4.15)	1090 (9.15)	2.66 (2.42 to 2.93)
≥42	201 (1.23)	298 (2.32)	2.15 (1.78 to 2.61)	432 (1.28)	441 (3.70)	3.26 (2.81 to 3.77)
Unknown	1666 (10.23)	1089 (8.47)	1.15 (1.05 to 1.25)	7641 (22.66)	2225 (18.68)	1.16 (1.09 to 1.24)
Body mass index:						
<20	379 (2.33)	123 (0.96)	0.61 (0.49 to 0.76)	1209 (3.59)	192 (1.61)	0.67 (0.57 to 0.79)
20-24.9	3990 (24.51)	1963 (15.27)	1	9909 (29.39)	2262 (18.99)	1
25-29.9	6358 (39.05)	4955 (38.54)	1.55 (1.45 to 1.66)	10 265 (30.44)	4214 (35.38)	1.76 (1.66 to 1.87)
≥30	3702 (22.74)	4560 (35.46)	2.19 (2.04 to 2.36)	3710 (11.00)	2616 (21.96)	2.71 (2.52 to 2.90)
Unknown	1851 (11.37)	1257 (9.78)	1.56 (1.42 to 1.71)	8627 (25.58)	2626 (22.05)	1.49 (1.39 to 1.59)
Medical conditions:						
Ischaemic heart disease	3670 (22.54)	3289 (25.58)	1.19 (1.12 to 1.26)	3046 (9.03)	1634 (13.72)	1.54 (1.43 to 1.66)
Hyperlipidaemia	3391 (20.83)	3305 (25.70)	1.14 (1.08 to 1.21)	2537 (7.52)	1274 (10.70)	1.29 (1.20 to 1.39)
Renal failure	338 (2.08)	727 (5.65)	2.32 (2.03 to 2.66)	129 (0.38)	220 (1.85)	3.78 (3.00 to 4.76)
Heart failure	808 (4.96)	1348 (10.48)	2.32 (2.11 to 2.56)	614 (1.82)	794 (6.67)	4.06 (3.60 to 4.58)

*Adjusted for sex, age, calendar year, and visits to general practitioner.

†1 unit=10 ml of pure ethanol (8 g of alcohol).

Table 2| Relative risk of gout associated with use of antihypertensive drugs stratified by presence of hypertension

	Hypertension			No hypertension			
Use of antihypertensives	**No (%) of controls (n=16 280)**	**No (%) of cases (n=12 858)**	**Adjusted relative risk* (95% CI)**	**No (%) of controls (n=33 720)**	**No (%) of cases (n=11 910)**	**Adjusted relative risk* (95% CI)**	**P for interaction**
Diuretics:							
Never	6076 (37.32)	2761 (21.47)	1	30 161 (89.45)	9445 (79.30)	1	0.03
Current (<31 days)	6854 (42.10)	8159 (63.45)	2.36 (2.21 to 2.52)	1728 (5.12)	1762 (14.79)	3.01 (2.72 to 3.33)	
Recent (31-365 days)	1001 (6.15)	806 (6.27)	1.57 (1.40 to 1.76)	461 (1.37)	244 (2.05)	1.65 (1.38 to 1.97)	
Past (>365 days)	2349 (14.43)	1132 (8.80)	0.98 (0.90 to 1.08)	1370 (4.06)	459 (3.85)	1.05 (0.93 to 1.18)	
β blockers:							
Never	8089 (49.69)	5079 (39.50)	1	29 711 (88.11)	9933 (83.40)	1	0.04
Current (<31 days)	4749 (29.17)	4967 (38.63)	1.48 (1.40 to 1.57)	1620 (4.80)	962 (8.08)	1.16 (1.04 to 1.29)	
Recent (31-365 days)	671 (4.12)	625 (4.86)	1.20 (1.06 to 1.36)	405 (1.20)	204 (1.71)	1.12 (0.93 to 1.36)	
Past (>365 days)	2771 (17.02)	2187 (17.01)	1.03 (0.96 to 1.11)	1984 (5.88)	811 (6.81)	0.97 (0.88 to 1.06)	
Calcium channel blockers:							
Never	9127 (56.06)	6685 (51.99)	1	31 768 (94.21)	10 951 (91.95)	1	0.17
Current (<31 days)	4603 (28.27)	3388 (26.35)	0.87 (0.82 to 0.93)	997 (2.96)	447 (3.75)	0.84 (0.73 to 0.97)	
Recent (31-365 days)	651 (4.00)	670 (5.21)	1.03 (0.91 to 1.17)	194 (0.58)	95 (0.80)	0.72 (0.55 to 0.96)	
Past (>365 days)	1899 (11.66)	2115 (16.45)	1.13 (1.04 to 1.23)	761 (2.26)	417 (3.50)	0.96 (0.82 to 1.11)	
Angiotensin converting enzyme inhibitors:							
Never	9238 (56.74)	5630 (43.79)	1	32 103 (95.20)	10 412 (87.42)	1	0.04
Current (<31 days)	4733 (29.07)	4818 (37.47)	1.24 (1.17 to 1.32)	1136 (3.37)	1085 (9.11)	1.37 (1.21 to 1.54)	
Recent (31-365 days)	598 (3.67)	709 (5.51)	1.32 (1.16 to 1.50)	162 (0.48)	144 (1.21)	1.36 (1.05 to 1.77)	
Past (>365 days)	1711 (10.51)	1701 (13.23)	1.08 (0.99 to 1.19)	319 (0.95)	269 (2.26)	1.11 (0.90 to 1.38)	
Losartan:							
Never	15 551 (95.52)	12 141 (94.42)	1	33 596 (99.63)	11 797 (99.05)	1	0.20
Current (<31 days)	482 (2.96)	397 (3.09)	0.81 (0.70 to 0.94)	92 (0.27)	72 (0.60)	0.90 (0.62 to 1.30)	
Recent (31-365 days)	77 (0.47)	83 (0.65)	0.96 (0.68 to 1.35)	16 (0.05)	11 (0.09)	0.51 (0.21 to 1.25)	
Past (>365 days)	170 (1.04)	237 (1.84)	1.10 (0.89 to 1.37)	16 (0.05)	30 (0.25)	1.74 (0.88 to 3.43)	
Non-losartan angiotensin II receptor blockers:							
Never	15 073 (92.59)	11 270 (87.65)	1	33 581 (99.59)	11 728 (98.47)	1	0.72
Current (<31 days)	895 (5.50)	1223 (9.51)	1.29 (1.16 to 1.43)	108 (0.32)	145 (1.22)	1.40 (1.04 to 1.88)	
Recent (31-365 days)	134 (0.82)	150 (1.17)	1.05 (0.81 to 1.35)	15 (0.04)	16 (0.13)	1.24 (0.55 to 2.80)	
Past (>365 days)	178 (1.09)	215 (1.67)	1.13 (0.91 to 1.41)	16 (0.05)	21 (0.18)	1.20 (0.56 to 2.58)	

*Adjusted for sex, age, calendar year, number of visits to a general practitioner, body mass index, alcohol intake, ischaemic heart disease, hyperlipidaemia, diabetes, chronic renal failure and heart failure, and simultaneously for the other antihypertensive drug classes.

Table 3| Relative risk of gout associated with duration of use of antihypertensive drugs among current users, stratified by presence of hypertension

	Hypertension			No hypertension		
Duration of antihypertensive use	**No (%) of controls (n=16 280)**	**No (%) of cases (n=12 858)**	**Adjusted relative risk* (95% CI)**	**No (%) of controls (n=33 720)**	**No (%) of cases (n=11 910)**	**Adjusted relative risk* (95% CI)**
Diuretics:						
<1 year	1751 (10.76)	1566 (12.18)	1.79 (1.63 to 1.96)	570 (1.69)	436 (3.66)	2.26 (1.94 to 2.62)
1-1.9 years	1160 (7.13)	1295 (10.07)	2.27 (2.05 to 2.51)	309 (0.92)	290 (2.43)	2.77 (2.28 to 3.35)
≥2 years	3943 (24.22)	5298 (41.20)	2.62 (2.44 to 2.82)	849 (2.52)	1036 (8.70)	3.63 (3.20 to 4.12)
P for trend			<0.001			<0.001
β blockers:						
<1 year	933 (5.73)	861 (6.70)	1.36 (1.21 to 1.51)	503 (1.49)	262 (2.20)	1.10 (0.93 to 1.32)
1-1.9 years	691 (4.24)	732 (5.69)	1.52 (1.35 to 1.72)	264 (0.78)	188 (1.58)	1.23 (0.98 to 1.54)
≥2 years	3125 (19.20)	3374 (26.24)	1.47 (1.38 to 1.57)	853 (2.53)	512 (4.30)	1.18 (1.03 to 1.35)
P for trend			0.15			0.24
Calcium channel blockers:						
<1 year	1180 (7.25)	1004 (7.81)	1.04 (0.94 to 1.15)	269 (0.80)	116 (0.97)	0.81 (0.63 to 1.04)
1-1.9 years	737 (4.53)	549 (4.27)	0.89 (0.78 to 1.00)	156 (0.46)	79 (0.66)	0.92 (0.68 to 1.27)
≥2 years	2686 (16.50)	1835 (14.27)	0.77 (0.71 to 0.83)	572 (1.70)	252 (2.12)	0.80 (0.67 to 0.96)
P for trend			<0.001			0.87
Angiotensin converting enzyme inhibitors:						
<1 year	1198 (7.36)	1058 (8.23)	1.09 (0.99 to 1.20)	360 (1.07)	276 (2.32)	1.27 (1.05 to 1.53)
1-1.9 years	801 (4.92)	719 (5.59)	1.08 (0.96 to 1.22)	219 (0.65)	190 (1.60)	1.38 (1.09 to 1.74)
≥2 years	2734 (16.79)	3041 (23.65)	1.32 (1.23 to 1.42)	557 (1.65)	619 (5.20)	1.40 (1.20 to 1.63)
P for trend			<0.001			0.71
Losartan:						
<1 year	127 (0.78)	117 (0.91)	0.97 (0.74 to 1.27)	25 (0.07)	15 (0.13)	0.71 (0.35 to 1.45)
1-1.9 years	96 (0.59)	80 (0.62)	0.86 (0.62 to 1.18)	22 (0.07)	14 (0.12)	1.04 (0.49 to 2.22)
≥2 years	259 (1.59)	200 (1.56)	0.70 (0.57 to 0.86)	45 (0.13)	43 (0.36)	0.84 (0.52 to 1.37)
P for trend			0.02			0.185
Non-losartan angiotensin II receptor blockers:						
<1 year	316 (1.94)	381 (2.96)	1.20 (1.02 to 1.42)	46 (0.14)	66 (0.55)	1.54 (1.00 to 2.35)
1-1.9 years	203 (1.25)	275 (2.14)	1.30 (1.06 to 1.59)	26 (0.08)	33 (0.28)	1.30 (0.73 to 2.32)
≥2 years	376 (2.31)	567 (4.41)	1.33 (1.14 to 1.54)	36 (0.11)	46 (0.39)	1.12 (0.68 to 1.86)
P for trend			0.67			0.12

*Adjusted for sex, age, calendar year, number of visits to general practitioner, body mass index, alcohol intake, ischaemic heart disease, hyperlipidaemia, diabetes, chronic renal failure, heart failure, and simultaneously for the other antihypertensive drug classes.

Table 4| **Relative risk of gout associated with daily dose of antihypertensive agents among current users, stratified by presence of hypertension**

	Hypertension			No hypertension		
Daily dose	No (%) of controls (n=16 280)	No (%) of cases (n=12 858)	Adjusted relative risk* (95% CI)	No (%) of controls (n=33 720)	No (%) of cases (n=11 910)	Adjusted relative risk* (95% CI)
Diuretics:						
Low or medium dose	5630 (34.58)	6320 (49.15)	2.24 (2.09 to 2.39)	1361 (4.04)	1249 (10.49)	2.72 (2.44 to 3.03)
High dose	579 (3.56)	971 (7.55)	2.99 (2.63 to 3.40)	263 (0.78)	419 (3.52)	4.16 (3.45 to 5.02)
Unknown	645 (3.96)	868 (6.75)	2.76 (2.43 to 3.12)	104 (0.31)	94 (0.79)	3.60 (2.63 to 4.92)
β blockers:						
Low or medium dose	3234 (19.86)	3156 (24.55)	1.39 (1.30 to 1.49)	1258 (3.73)	697 (5.85)	1.15 (1.02 to 1.29)
High dose	1377 (8.46)	1677 (13.04)	1.59 (1.46 to 1.74)	319 (0.95)	237 (1.99)	1.14 (0.94 to 1.39)
Unknown	138 (0.85)	134 (1.04)	1.63 (1.25 to 2.13)	43 (0.13)	28 (0.24)	1.69 (0.99 to 2.90)
Calcium channel blockers:						
Low or medium dose	2298 (14.12)	1757 (13.66)	0.90 (0.84 to 0.98)	626 (1.86)	272 (2.28)	0.83 (0.70 to 0.99)
High dose	2271 (13.95)	1596 (12.41)	0.80 (0.74 to 0.87)	359 (1.06)	170 (1.43)	0.84 (0.67 to 1.04)
Unknown	34 (0.21)	35 (0.27)	1.80 (1.07 to 3.04)	12 (0.04)	5 (0.04)	1.26 (0.36 to 4.38)
Angiotensin converting enzyme inhibitors:						
Low or medium dose	1998 (12.27)	1848 (14.37)	1.23 (1.14 to 1.33)	657 (1.95)	538 (4.52)	1.33 (1.15 to 1.54)
High dose	2665 (16.37)	2914 (22.66)	1.23 (1.15 to 1.33)	465 (1.38)	532 (4.47)	1.39 (1.18 to 1.63)
Unknown	70 (0.43)	56 (0.44)	0.96 (0.65 to 1.41)	14 (0.04)	15 (0.13)	1.84 (0.81 to 4.21)
Losartan:						
Low or medium dose	287 (1.76)	245 (1.91)	0.88 (0.73 to 1.06)	77 (0.23)	61 (0.51)	0.93 (0.63 to 1.39)
High dose	190 (1.17)	149 (1.16)	0.66 (0.52 to 0.84)	15 (0.04)	10 (0.08)	0.52 (0.22 to 1.26)
Unknown	5 (0.03)	3 (0.02)	0.66 (0.15 to 2.89)	0 (0.00)	1 (0.01)	—
Non-losartan angiotensin II receptor blockers:						
Low or medium dose	582 (3.57)	712 (5.54)	1.20 (1.06 to 1.36)	89 (0.26)	112 (0.94)	1.24 (0.90 to 1.72)
High dose	298 (1.83)	486 (3.78)	1.40 (1.19 to 1.65)	18 (0.05)	32 (0.27)	1.89 (0.98 to 3.61)
Unknown	15 (0.09)	25 (0.19)	1.14 (0.58 to 2.25)	1 (0.01)	1 (0.01)	0.85 (0.03 to 24.19)

*Adjusted for sex, age, calendar year, number of visits to general practitioner, body mass index, alcohol intake, ischaemic heart disease, hyperlipidaemia, diabetes, chronic renal failure, heart failure, and simultaneously for the other antihypertensive drug classes.